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(57) Abstract

The invention relates to long-acting pharmaceutical compositions from which the release of the active compound increases exponentially, and to a process for their preparation. The composition, preferably a tablet, comprises a rapid releasing core and a slow-releasing coat surrounding that core.

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CONTROLLED RELEASE PHARMACEUTICAL PREPARATIONS

The invention relates to long-acting pharmaceutical preparations from which the release of the active compound increases exponentially, and to a process for their preparation.

In developing oral long-acting pharmaceutical preparations it is usual aim to design a preparation which have a constant rate of release of active compound (zero order kinetics). Often such preparations have been made by coating a tablet with a polymer which is insoluble in the intestine and by adjusting the permeability of such coating with a suitable water soluble polymer. The coating process is however expensive and often requires the use of organic solvents.

An easier alternative to coated tablets is a matrix tablet. A matrix tablet is prepared by mixing the active compound with a suitable polymer to produce an uniform mixture. The polymer used is either hydrophobic (insoluble), in which case the active compound is released by diffusion through the pores in the matrix, or hydrophilic (gel forming), in which case the release occurs mainly as the polymer is gradually eroded. In matrix tablets, however, the rate of release usually decreases as a function of time. Typically, the released amount of active compound is proportional to the square root of time or follows primarily first order kinetics.

The attempt to design a long-acting tablet which as close as possible follows zero order kinetics is based on the idea that zero order release result in constant drug levels in the body. The assumption is that absorption conditions in the gastrointestinal tract do not change while the preparation releases active compound. However, this is not always true in oral medical treatment.

When an insoluble tablet is taken orally into the empty stomach, the tablet stays there for 0-2 h. It is then passed through the small intestine in 2-4 hours and is in the lowest part of the small intestine or in the large intestine 2-6 hours after ingestion. Most drugs show greatest absorption in the upper parts of the small intestine, in the duodenum. In the lower part of gastrointestinal tract the absorption decreases and is lowest in the large intestine. This is

influenced by the structure and action of gastrointestinal tract as well as the viscosity of the contents of the intestine.

The physiology of the gastrointestinal tract as described above normally means that, if the absorption of drug from a long-acting tablet is wished to be nearly constant, the rate of drug release must increase with time as the tablet moves forward in the gastrointestinal tract, i.e. the release must be exponential.

Attempt to constant absorption (and therefore to zero order release kinetics) is also based on the assumption that medical treatment is optimal when the drug concentration in plasma is as constant as possible during the day. However, numerous diseases are known which have a marked diurnal rhythm. Thus the drug concentration in plasma should also vary in the same rhythm during the treatment.

An example of a disease having a diurnal rhythm is hypertension. Blood pressure is at its lowest at early night and highest early in the morning. Similarly attacks in early morning are typical for pulmonary asthma, and morning stiffness is one symptom of rheumatism and subject to medical treatment. With conventional preparations the plasma concentrations are higher at early night than in early morning when the situation should be the opposite. Thus the optimal solution is a long-acting preparation to be taken in the evening and which have a slowly increasing release rate.

U.S. Patent No. 4,933,186 describes a two layer long-acting tablet with a rapid release core. The purpose of the coat is to delay the release of the active compound from the core. Optionally the coat may be further coated with a layer of active compound. In this case the release is effected in two bursts. Such preparations are not suitable for treatment wherein the active compound must be released in a slowly increasing way.

According to this invention it is possible to prepare simple long-acting oral compositions in which the release of active compound increases as a function of time (exponentially). Characteristically these compositions do not release the active compound discontinuously in bursts but primarily following an exponential release pattern.

According to the invention it is possible to adjust the release of an active compound to the diurnal rhythm of certain diseases. Such diseases are for example hypertension and pulmonary asthma. The compositions accord-

ing to the invention are also suitable for active compounds which show greater absorption in lower parts of gastrointestinal tract (e.g. in the large intestine) than in upper parts (e.g. in stomach or the small intestine) or which are designed to act mainly locally in the large intestine. The compositions are suitable for releasing poorly soluble drugs as well as water soluble drugs. Hitherto the formulation of poorly soluble active compounds into long-acting preparations has been especially troublesome. Furthermore the compositions according to the invention are simple and easy to prepare compared to many other long-acting preparations. The preparation process do not either require the use of hazardous material, e.g. organic solvents.

The composition according to invention, preferably a tablet, comprises: (a) a core containing an active compound in rapid release form, and (b) a coat surrounding the core, the coat containing an active compound in slow-release form, wherein 50 - 99 % of the total active compound is in the core.

The core is a conventional rapid release tablet comprising besides an active compound suitable pharmaceutically acceptable auxiliaries, e.g., fillers, lubricants and binders. Examples of such auxiliaries are lactose, polyvinylpyrrolidone, magnesium stearate and talc.

The coat comprises besides an active compound a polymer controlling the rate of release and optionally auxiliaries such as described above. Preferable polymers are hydrophilic, gel forming polymers, especially hydroxypropylmethylcellulose, which is commercially available in various types, e.g., Methocel K100 (m.w. 26000 g/mol), Methocel K4M (m.w. 86000 g/mol), Methocel K15M (m.w. 120000 g/mol) and Methocel K100M. Other hydrophilic polymers include, for example, methylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose and sodium alginate.

The tablet contains in the core 50 - 99 %, preferably about 55 - 80 %, more preferably about 60 - 70 %, of the total content of active compound. About 30 - 70 %, preferably about 40 - 60 %, of the tablet weight is polymer depending on the desired total release rate. The total tablet diameter is preferably about 7 - 15 mm.

The release profile may be adjusted on the one hand by the amount and quality of the polymer in the coat, on the other hand by the relative amount of the active compound between the core and the coat. When the active compound is furosemide or salbutamol sulphate, the suitable ratio of ac-

tive compound between the coat and the core is, for example, 1:2. Suitable polymer amount and type in the coat as well as suitable coat/core ratio for any active compound may be determined by simple dissolution tests described in pharmacopoeias, e.g., the paddle method according to US XXII. The effect of polymer amount and quality in the coat is demonstrated in Figures 1 and 3.

The active compound may be a water soluble or poorly soluble compound. When poorly soluble acidic compounds such as furosemide are used, may both the core and the coat contain weakly basic inorganic salt, e.g., potassium carbonate. When water soluble active compounds such as salbutamol sulphate are used, no basic salt is needed.

The compositions according to the invention may be prepared easily using conventional tablet-coating press machines. The core may be prepared according to usual tablet processes by pressing powder mixtures or granules. Powders needed for the core are mixed using known powder mixers. Produced mixture may be granulated with the aid of known processes and devices used in preparing tablet mass. The powder mixture may, for example, be moistened with polymer solution or dispersion, e. g., with polyvinylpyrrolidone solution, then sieved into suitable granulate size and dried. Granulation may also be done by spraying powder mixture with solutions or dispersions in fluidized bed granulator. The coat is pressed around the core with the aid of a tablet press or a special tablet-coating press, wherein the coat material may consist of flowing powder mixtures or granules. The invention is further illustrated with the aid of following examples.

Example 1.

<u>Core</u>	
Furosemide	40 mg
Potassium carbonate	20 mg
Lactose	40 mg
Polyvinylpyrrolidone (Kollidon K 25) 10% solution	q.s.
Magnesium stearate	1 %
Talc	2 %

<u>Coat</u>	
Furosemide	20 mg
Potassium carbonate	10 mg
Hydroxypropylmethylcellulose (Methocel K100)	80 mg
Magnesium stearate	1 %
Talc	2 %

Example 2.

As Example 1 but hydroxypropylmethylcellulose amount in the coat is 100 mg.

Example 3.

As Example 1 but hydroxypropylmethylcellulose amount in the coat is 120 mg.

Example 4.

Core	
Salbutamol sulphate	16 mg
Lactose	60 mg
Polyvinylpyrrolidone (Kollidon K 25) 10% solution	q.s.
Magnesium stearate	1 %
Talc	2 %
Coat	
Salbutamol sulphate	8 mg
Hydroxypropylmethylcellulose (Methocel K100)	80 mg
Magnesium stearate	1 %
Talc	2 %

Example 5.

As Example 4 but hydroxypropylmethylcellulose amount in the coat is 100 mg.

Example 6.

As Example 4 but hydroxypropylmethylcellulose amount in the coat is 120 mg.

Example 7.

As Example 4 but the polymer is Methocel K4M.

Example 8.

As Example 5 but the polymer is Methocel K4M.

Example 9.

As Example 6 but the polymer is Methocel K4M.

Example 10.

As Example 4 but the polymer is Methocel K4M and its amount is 160 mg.

The tablets described in the Examples were prepared by mixing powders needed for a batch of desired size in conventional mixers. The powder mixture for the core was moistened with polyvinylpyrrolidone solution and

granulated by pressing through a 1.2 mm sieve. Granulate was dried in 30°C overnight. Dry granulate was sieved and 0.5 - 1.2 mm fraction was used for pressing tablets using 5 - 6 mm concave punchs and about 20 kN compressional force. The core tablet was coated with coating material in a tablet press using 9 - 11 mm concave punchs and 10 - 15 kN compressional force.

The release of an active compound from tablets may be determined by dissolution tests described in pharmacopoeias, e.g., the paddle method according to US XXII.

Figure 1 shows the release of furosemide from the tablets of Examples 1-3. It can be seen that the release curves are primarily exponential up to 80 - 90 % of the total release for all three tablets. Furthermore the figure shows that the position of the release curve may be systematically adjusted with the aid of the polymer amount in the coat.

Figure 2 (tablet of Ex. 2) shows that the compositions according to the invention act as long-acting preparations also in in-vivo conditions. Absorption tests were performed using dogs and furosemide concentrations in plasma were determined by liquid chromatography.

Figure 3 shows that low soluble drug may be replaced by water soluble drug (here salbutamol sulphate) and nevertheless the release curve remains exponential.

Claims

1. Oral long-acting composition comprising: (a) a core which contains an active compound in rapid release form, and (b) a coat surrounding the core, the coat containing an active compound in slow-release form, wherein 50 - 99 % of the total active compound is in the core.

2. A composition according to Claim 1, wherein the core comprises an active compound and pharmaceutical auxiliaries.

3. A composition according to any of Claims 1-2, wherein the coat comprises an active compound and a release controlling polymer.

4. A composition according to Claim 3, wherein the polymer is hydrophilic gel forming polymer.

5. A composition according to Claim 4, wherein the polymer is hydroxypropylmethylcellulose.

6. A composition according to Claim 5, wherein the molcular weight of the hydroxypropylmethylcellulose is 20000 - 150000 g/mol.

7. A composition according to any of Claims 1-6, wherein about 55 - 80 %, more preferably about 60 - 70 %, of the total active compound is in the core.

8. A composition according to any of Claims 1-7, wherein 30 - 70 %, preferably about 40 - 60 %, of the total composition weight is polymer.

9. A composition according to any of Claims 1-8, wherein the active compound is a poorly water soluble weak acid.

10. A composition according to Claim 9, wherein the composition also comprises basic salt such as potassium carbonate.

11. A composition according to any of Claims 1-10, wherein the active compound is furosemide.

12. A composition according to any of Claims 1-8, wherein the active compound is a water soluble salt.

13. A composition according to Claim 12, wherein the active compound is salbutamol sulphate.

14. A composition according to any of Claims 1-13, wherein the composition is a two layer tablet.

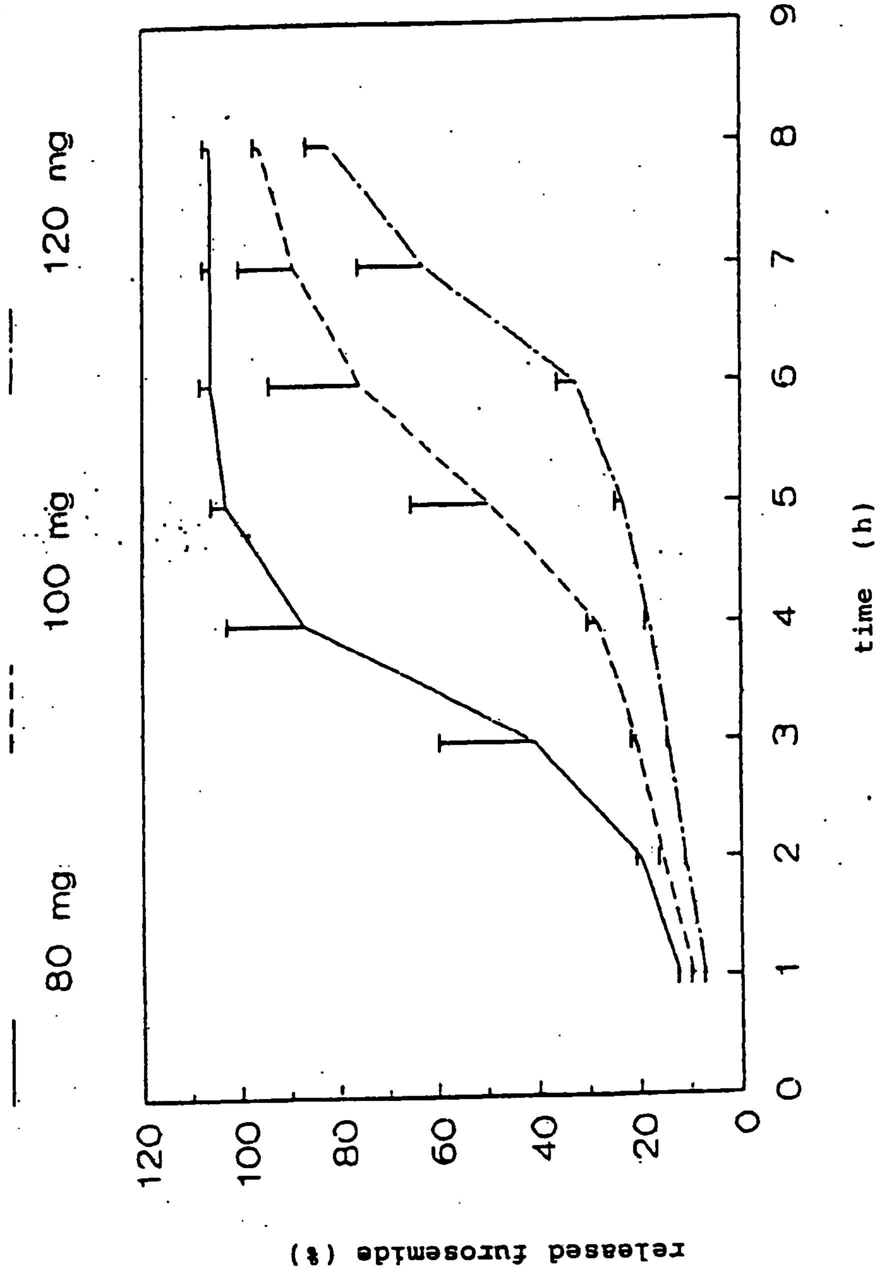
HPMC amount
80 mg
100 mg
120 mg
released furosemide (%)
time (h)
0
20
40
60
80
100
120
0
1
2
3
4
5
6
7
8
9

FIG. 1

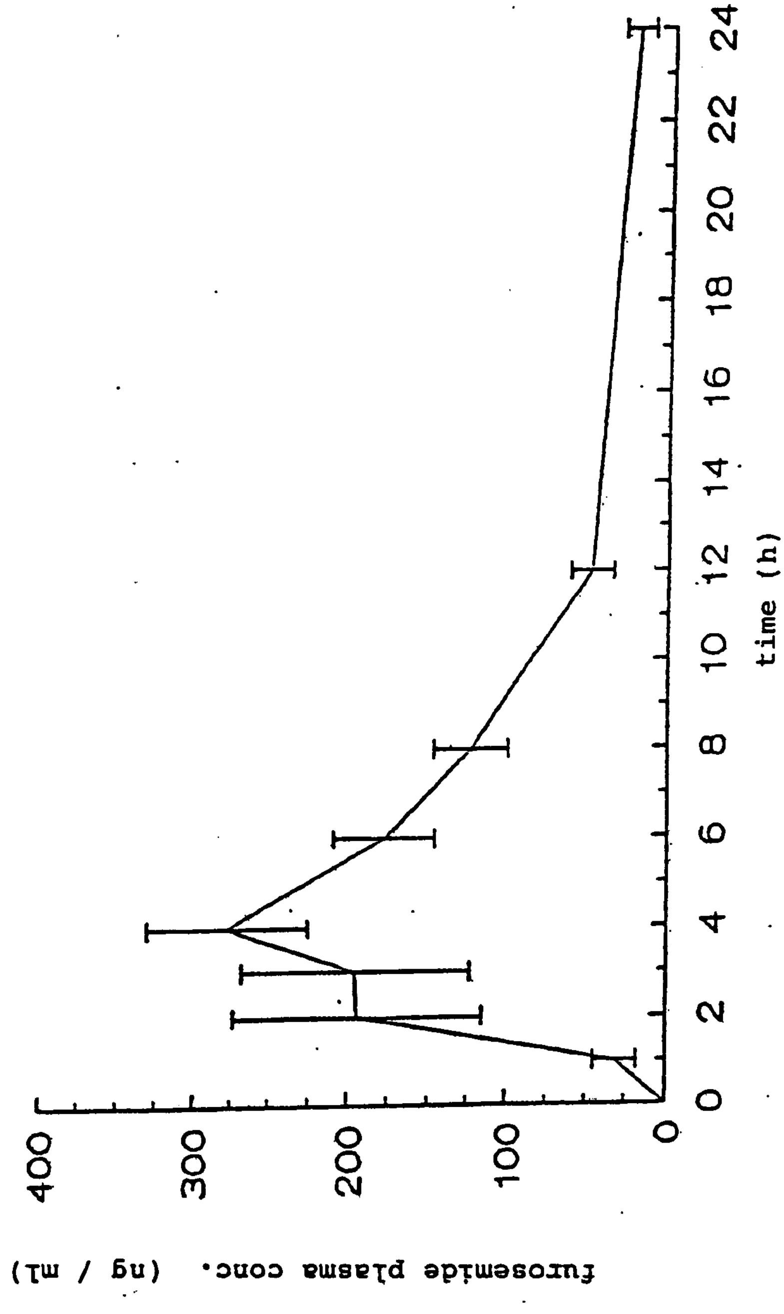
furosemide plasma conc. (ng / ml)
0
100
200
300
400
time (h)
0
2
4
6
8
10
12
14
16
18
20
22
24

FIG. 2

HPMC amount

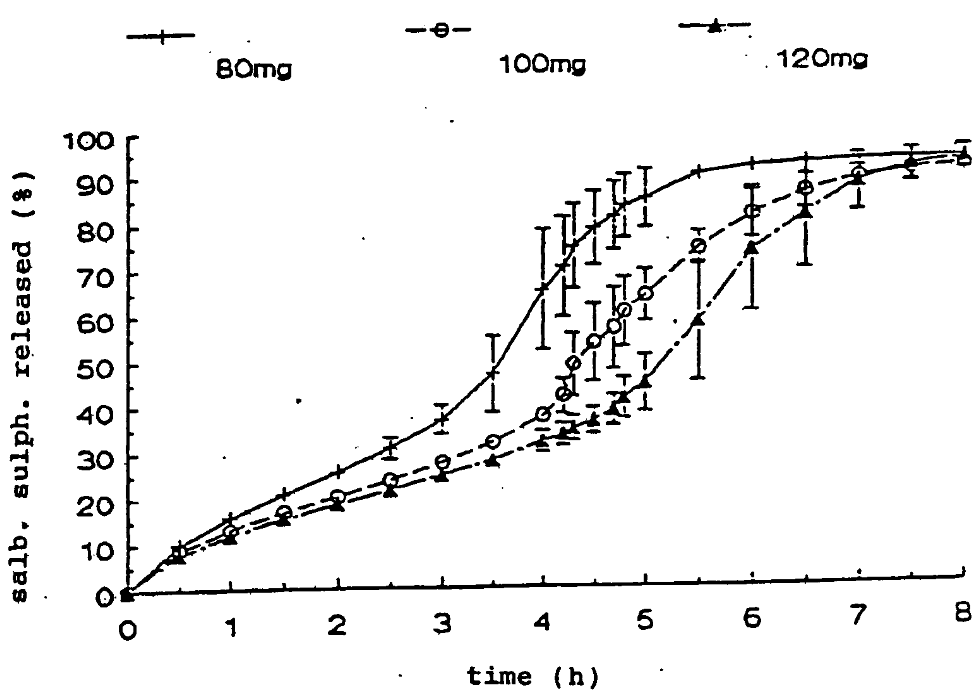

FIG. 3

INTERNATIONAL SEARCH REPORT

International Application No PCT/FI 92/00242

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/24

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[°]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	EP,A,0 384 514 (NORWICH EATON PHARMACEUTICALS) 29 August 1990 see page 3, line 22 - line 24 see page 4, line 24 - line 51 see page 5 - page 7; examples I,II see claims 1,5 ---	1-14
Y	US,A,3 558 768 (KLIPPEL K.R. ET AL) 26 January 1971 see column 2, line 4 - line 32 see column 3; example 1 ---	1-9,12, 14
Y	GB,A,2 137 493 (DR. KISHAN NARAIN MATHUR) 10 October 1984 see page 1, line 38 - line 46 ---	10,11
	-/--	

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16 NOVEMBER 1992	07. 12. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	BOULOIS D.

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
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A	CHEMICAL ABSTRACTS, vol. 90, no. 20, 14 May 1979, Columbus, Ohio, US; abstract no. 157017s, BELINDA D. ET AL 'Diuretic effect of a combined preparation of frusemide and slow-release potassium chloride' page 297 ;column 1 ; & Curr. Med. Res.Opin. 1978 5(9) 739-42 see abstract	10,11
A	EP,A,0 299 211 (BAYER AG) 18 January 1989 see page 5 - page 6; example 1	1
A	BE,A,658 905 (RICHARDSON MERRELL INC) 27 July 1965 see page 8; example 1	1
A	GB,A,2 123 291 (GRUPPO LEPETIT SPA) 1 February 1984 see page 2 - page 4; examples 1-3	1

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US-A-3558768	26-01-71	None		
GB-A-2137493	10-10-84	None		
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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